Br. J. Anaesth. (1982), 54, 1191

I.V. LABETALOL IN THE TREATMENT OF HYPERTENSION FOLLOWING CORONARY-ARTERY SURGERY

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SUMMARY

The cardiovascular effects of incremental fixed i.v. doses of labetalol were evaluated in 10 normovolaemic sedated patients presenting with hypertension and tachycardia in the early period after myocardial revascularization. A first dose of 20 mg was sufficient to provoke a significant ($P < 0.01$) mean decrease in systolic (−9.3%), diastolic (−8.2%) and mean arterial (−7.9%) pressure (AP) and in the rate–pressure product (RPP) (−13.1%). The mean heart rate (HR) did not change significantly, but a linear correlation could be established between the change at 2 min and the value before injection ($r = 0.73$). A second dose of labetalol 40 mg given 5 min later did not decrease AP further, but a significant decrease in HR was noted. A marked difference in the individual response among patients was found as the range of effective total doses per kg body weight was 0.6–4.1 mg kg^{-1} (mean 2.2). Apart from one patient, no patient needed vagolytic or sympathomimetic drugs to oppose the alpha or beta actions of labetalol during the 24-h follow-up period.

The occurrence of hypertension and tachycardia after myocardial revascularization has been observed in 30–60% of patients undergoing coronary artery surgery (Estafanous et al., 1973; Hoar, Hickey and Ullyot, 1976; Roberts et al., 1977; Fouad, Estafanous and Tarazi, 1978). This syndrome appears usually within the first 2 h after the patient has returned to the intensive care unit (ICU) and lasts about 4–8 h. It can lead to various and severe complications, including haemorrhage, arrhythmia, myocardial ischaemia or infarction. Several treatments have been proposed, including vasodilator therapy (Estafanous et al., 1973; Roberts et al., 1977; Fouad, Estafanous and Tarazi, 1978), extradural anaesthesia (Hoar, Hickey and Ullyot, 1976), preoperative stellate ganglion blockade (Bidwai et al., 1979). Beta-adrenergic blocking agents seem less successful; i.v. propranolol was shown to increase total peripheral resistance, partly in response to the reduction of cardiac output and also possibly because of unopposed alpha stimulation (Ulrych et al., 1968).

Labetalol is a drug which competitively blocks both alpha- and beta-adrenoceptors (Farmer et al., 1972; Brittain and Levy, 1976), and which has an elimination plasma half-life of 4.0 ± 0.5 h in man (Martin, Hopkins and Bland, 1976). It has the advantage over pure vasodilators of counteracting the baroreceptor reflex increase in HR and cardiac output elicited by the AP decrease. On the other hand, its alpha-adrenoceptor blocking property decreases left ventricular filling pressure, which can be increased by the use of pure beta-adrenoceptor antagonists (Peter et al., 1978). These unique pharmacological properties make labetalol particularly attractive as an antihypertensive agent, especially in patients suffering from coronary artery disease in whom the aim is to reduce myocardial oxygen consumption. As the latter can be estimated from the rate–pressure product (RPP) (Gobel et al., 1978), labetalol, acting on both components of this product, will improve angina pectoris by diminishing myocardial oxygen consumption.

The purpose of this study was to evaluate the cardiovascular effects of incremental fixed i.v. doses of labetalol in patients presenting with hypertension and tachycardia in the early period following myocardial revascularization.

PATIENTS AND METHODS

The study was approved by the Committee on Human Research of our institution.

Patients

The study was begun in the ICU, during the first 2 h after operation in 10 patients who presented with hypertension and tachycardia, as defined below,

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0007–0912/82/111191–06 $01.00

TABLE I. *Patients studied and haemodynamic data before operation (n = 10). AP = arterial pressure; RPP = rate–pressure product; LVEDP = Left ventricular end-diastolic pressure (catheterism laboratory data)*

	Mean ± SD	Range
Age (yr)	57 ± 9	45–71
Weight (kg)	81 ± 9	69–95
Systolic AP (kPa)	20 ± 3	18–25
Diastolic AP (kPa)	12 ± 1.6	11–15
Heart rate (beat min^{-1})	72 ± 8	55–80
RPP (kPa min^{-1})	1423 ± 200	1100–1727
LVEDP (kPa)	2.5 ± 0.8	1.6–3.7
Ejection fraction (%)	57 ± 12	30–70

after an elective aortocoronary bypass operation. The clinical data are reported in table I. All patients were males and coronary artery disease had been recognized clinically and confirmed before operation with coronary arteriography. All but one patient were receiving adequate beta-blocker treatment (oxprenolol or pindolol), but did not receive a beta-blocker the day of surgery, and three patients were known to be hypertensive before operation.

Anaesthesia and postoperative management

The anaesthetic technique and the postoperative management were identical in all patients. Anaesthesia was induced with flunitrazepam 0.03 mg kg^{-1} and pancuronium bromide 0.1 mg kg^{-1} and maintained with 40% oxygen in 60% nitrous oxide and fentanyl (total dose 1.0–1.5 mg) and droperidol 10–15 mg. Recovery from cardiopulmonary bypass was achieved without difficulty in all patients and no vasopressor agent was used after coronary bypass.

The tracheal tube was kept in place and the lungs artificially ventilated for the first 12 h after operation to maintain arterial P_{CO_2} between 4.6–5.3 kPa and arterial P_{O_2} greater than 16 kPa. The electrocardiogram and AP were monitored continuously. Central venous pressure (c.v.p.), urine output and blood loss from the chest drains were recorded and all losses adequately replaced. Serum electrolytes and haematocrit were measured regularly and any abnormality corrected. The patients were sedated with small doses of morphine (mean dose ± SD) 5.3 ± 2.8 mg, diazepam 8.5 ± 5.2 mg and chlorpromazine 5.0 ± 2.6 mg i.v. over the first 4 h after operation.

A hypertension and tachycardia syndrome was defined as a sustained increase of RPP of more than 665 kPa min^{-1} greater than the patient's preoperative value, which ranged between 1100 and 1720, with systolic AP remaining greater than 16 kPa, excluding hypoxia, hypercarbia, shivering, fighting the ventilator or intolerance of the endotracheal tube, and which could not be reversed with simple sedation. The patients were admitted to the labetalol study if they maintained a hypertension and tachycardia syndrome for at least 30 min in spite of proper sedation and analgesia, as judged clinically.

Once the patient was in the study, the following variables were measured and recorded continuously on a four-channel polygraph: e.c.g. and HR by precordial derivation, systolic, diastolic and mean arterial pressure through a radial artery catheter and c.v.p. through a venous catheter with the zero reference point situated at mid-axillary level. RPP was calculated from the product of systolic AP × HR. The recording of the data was continued for 30 min, then the haemodynamic variables were noted every hour for a 24-h follow-up period. Secondary effects of labetalol and the need for vasoactive drugs were also recorded.

Labetalol was administered i.v. through a vein in the forearm over 15 s. First all patients were given a 20-mg dose. After 5 min, 40 mg was injected if hypertension and tachycardia were still present. Five minutes later, the patients who were still presenting with the syndrome received 80 mg of labetalol and this dose again every 5 min if indicated, until a total dose of labetalol 300 mg was achieved.

Statistical analyses

A Student's paired *t* test was used for statistical evaluation. The results are presented as means ± one standard deviation of the mean ($\bar{x} \pm$ SD).

RESULTS

The time courses of changes in arterial pressure, HR and the RPP are reported in figure 1. The first dose of labetalol 20 mg was sufficient to provoke a significant ($P < 0.01$) mean decrease in systolic (−9.3%), diastolic (−8.2%) and mean arterial (−7.9%) pressure and in RPP (−13.1%). Mean HR did not change significantly, but a linear correlation could be established between change at 2 min and the value before injection (fig. 2; $r = -0.73$). A similar correlation could be established between the change in systolic AP after 1 min and the value before injection: $r = -0.62$, $P < 0.05$ (fig. 3).

The second dose of labetolol given 5 min later did not decrease AP further, but a significant decrease in HR was noted. Eight of 10 patients required a

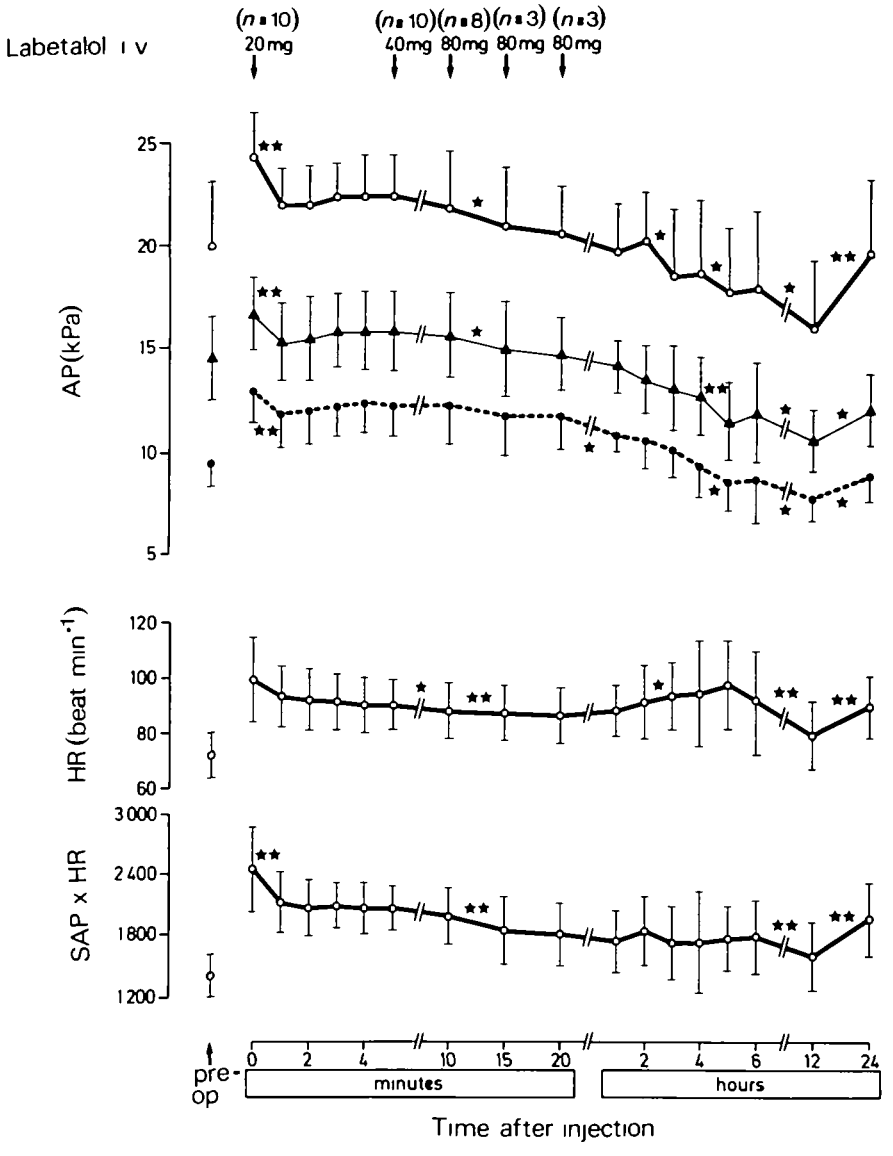

FIG 1. Haemodynamic effects of labetalol (mean ± SD, $n = 10$) given by incremental i.v bolus injection $^{*}P<0.05$, $^{**}P<0.01$. Arterial pressures: ○ = systolic, ▲ = mean, ● = diastolic.

third injection at 10 min and its haemodynamic effect was statistically significant. Three patients continued to manifest the hypertension and tachycardia syndrome after a total dose of 140 mg, but responded after two additional doses, each of 80 mg of labetalol. Thus there was a marked difference in the individual response among patients: the range of total doses per kg body weight was 0.6–4.1 mg kg^{-1} (mean 2.2) and there was no correlation between the need for labetalol and clinical and haemodynamic data before operation.

If the three "resistant" patients, who needed up to 300 mg of labetalol to attenuate their hypertension and tachycardia syndrome were excluded from the study, then the remainder, who received a mean dose of labetalol 1.46 ± 0.56 mg kg^{-1}, had a signific-

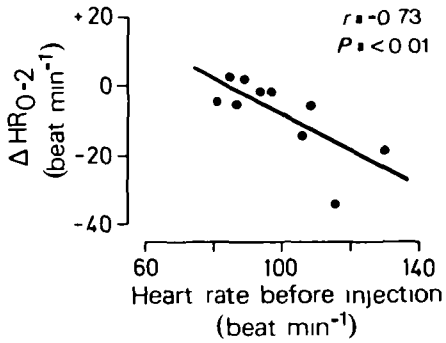

FIG. 2. Linear correlation between the decrease in heart rate during the first 2 min (ΔHR_{0-2}) after labetalol injection and its control value.

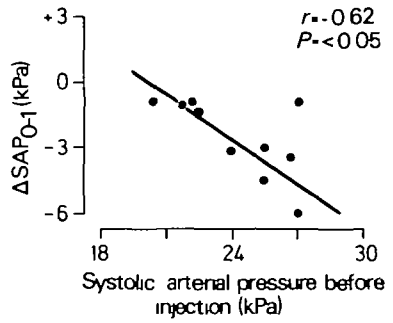

FIG. 3. Linear correlation between the decrease in systolic arterial pressure during the 1st min (ΔSAP_{0-1}) after labetalol injection and its control value

ant ($P<0.005$) percentage decrease in their haemodynamic variables of 11% (systolic), 10% (diastolic), 10% (mean AP) and 18% (RPP). In these patients, the correlation between the change in systolic AP after 1 min *v.* the value before injection was $r=0.91$ ($P<0.005$).

During the following hours AP continued to decrease spontaneously, even to values less than those before operation, with a smallest value almost always at 12 h after the start of the study, at which time the HR was also slowest. Twenty-four hours after the beginning of the investigation, AP values were about the same as those occurring before operation, while there persisted a relative faster HR (89 beat min^{-1}).

During the whole period of investigation, c.v.p. remained stable, with a mean value of 7 ± 4 cm H_2O before injection and ranging from 7 ± 4 to 10 ± 3 cm H_2O after labetalol. Rectal temperature at the beginning of the study was 36 ± 0.4°C and regularly increased to 38.5 ± 0.3°C 6 h later and to 38.1 ± 0.3°C at 24 h.

Apart from the haemodynamic changes produced by labetalol, we observed a reduction of ventricular extrasystolic beats in three patients. In one patient, unifocal ectopic ventricular beats appeared after the first 80-mg dose, lasting for 15 min. Another patient, the oldest of the group (71 yr), and who had the greatest left ventricular end-diastolic pressure value before operation (3.7 kPa) and the worst ejection fraction (30%), suddenly presented multifocal ventricular ectopic beats followed by bradycardia and ventricular fibrillation 90 min after the injection. After internal cardiac massage and defibrillation, the patient's heart recovered sinus rhythm for 30 min, then a similar episode occurred again and cardiopulmonary resuscitation was unsuccessful. The postmortem examination of the heart showed a large fresh anterior infarct.

Apart from this patient, no subject needed vagolytic or sympathomimetic drugs to oppose the alpha or beta actions of labetalol during the 24-h follow-up period, but three patients received small doses of dopamine (3-4 $\mu g\,kg^{-1}\,min^{-1}$) to improve renal perfusion between 6 and 18 h after operation.

DISCUSSION

Hypertension after myocardial revascularization with or without tachycardia in well ventilated and sedated patients is mainly caused by sympathetic hyperactivity with increased peripheral vascular resistance associated with increased plasma catecholamine concentrations (Roberts et al., 1977). In our institution, the frequency of this syndrome, as defined in this study, is 45% of 120 coronary bypass operations per year, which is in accordance with previous reports (Estafanous et al., 1973; Hoar, Hickey and Ullyot, 1976; Roberts et al., 1977; Fouad, Estafanous and Tarazi, 1978).

The theoretical advantage of labetalol in antagonizing simultaneously both alpha- and beta-adrenoceptor sites has been confirmed in our study. Labetalol 20 mg i.v. administered over 15 s has proved to be efficient in diminishing RPP clinically and statistically. The second (40 mg) and the third doses (80 mg) produced further progressive reductions of RPP. Three of 10 subjects, none hypertensive before operation, did not react to the loading dose of 140 mg and needed up to 300 mg to decrease RPP adequately.

An interesting feature of labetalol is the fact that individual changes are influenced by the degree of

resting sympathetic drive, thus more marked reductions in HR have been observed in patients with high HR values before injection, just as a greater decrease in systolic AP is found with high AP values before injection.

Our starting doses (20 mg) were far less than the dose recommended for chronically hypertensive subjects (Pearson and Havard, 1976; Cumming et al., 1979), but larger than those administered by Meretoja and others (1980) to a similar group of patients (mean total dose 15 mg). This difference in the sensitivity of such patients may be explained by the different times after the end of operation at which labetalol was given. Meretoja administered the drug, on average, 6 h after the end of extracorporeal circulation, a time at which the postmyocardial revascularization hypertension syndrome is frequently ceasing spontaneously, whatever treatment is applied. The AP of Meretoja's patients were significantly lower (mean 13.3 kPa) with one patient having a mean AP of 10 kPa associated with HR 59 beat min^{-1} before the labetalol injection. The difference between his and our findings is therefore not surprising: the earlier patients needed less adrenergic antagonists than those reported in the present study, in which labetalol was injected after operation during the first 2 h in more severely hypertensive patients.

The relative long duration of action of labetalol, lasting for 4–18 h (Pearson and Havard, 1976; Cumming et al., 1979), may be helpful in protecting the patient with coronary artery disease during the hypertensive period, but its use implies a careful monitoring of blood volume because physiological compensatory mechanisms may be attenuated by labetalol. It is difficult to determine if the fatal outcome in one patient in our series was precipitated by the use of labetalol, but it is noteworthy that this patient had a previous history of recurrent episodes of supraventricular tachycardia necessitating electrical shock and that he was the only patient not receiving beta-blockade treatment. Although Chiarello and others (1980) have demonstrated a protective effect of labetalol on myocardial cell necrosis after coronary artery occlusion in rats and studies in humans emphasized the beneficial effect of this drug in patients with angina pectoris (Besterman and Spencer, 1979) or acute myocardial infarction with systemic hypertension (Marx and Reid, 1979), once the arrhythmia in this patient had occurred, it was probably more difficult to perform successful cardiac resuscitation under labetalol than under a short-acting vasodilating agent. Thus, if the hypertension cannot be corrected by an i.v. dose of labetalol 100–150 mg administered over 10 min, then another mode of decreasing AP, for instance by i.v. sodium nitroprusside, should be considered.

We conclude that i.v. labetalol administered over 15 s in incremental fixed doses starting with 20 mg and, if necessary, doubling the dose after a 5-min interval until a total dose of 2 mg kg^{-1} is achieved, is safe and effective in producing a rapid reduction in RPP in patients presenting an acute postmyocardial revascularization hypertension syndrome. It would seem from our study that, if there is no effect after a 140-mg loading dose, greater doses of labetalol have little further beneficial action and can mask a slowly developing cardiovascular decompensation or may decrease the efficiency of a haemodynamic resuscitation.

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I.V. LABETALOL ZUR BEHANDLUNG DES HYPERTONUS NACH OPERATION AN DEN KORONARARTERIEN

ZUSAMMENFASSUNG

Die kardiovaskulären Wirkungen von Labetabol in einer festgelegten ansteigenden i.v. Dosierung wurden an zehn normovolamischen, sedierten Patienten gemessen, die in der frühen postoperativen Phase nach der myokardialen Revaskularisierung an Hypertonus und Tachykardie litten. Eine erste Dosis von 20 mg reichte aus, um eine signifikante durchschnittliche Senkung des systolischen (−9,3%), des diastolischen (−8,2%) und des mittleren arteriellen Druckes sowie des Produktes aus Frequenz und Druck (RRP) hervorzurufen (−13,1%). Die mittlere Herzfrequenz änderte sich nicht signifikant, aber es konnte eine lineare Korrelation hergestellt werden zwischen der Veränderung nach 2 min und dem Wert vor der Injektion ($r = 0{,}73$). Eine 2. Dosis von Labetalol (40 mg), die 5 min später verabreicht wurde, senkte den AD nicht weiter, aber es war ein signifikanter Abfall der HF festzustellen. In der individuellen Ansprechbarkeit bestand ein großer Unterschied zwischen den Patienten, da der Bereich der wirksamen Gesamtdosen pro kg KM von 0,6 bis 4,1 mg kg^{-1} (durchschnittlich 2,2) reichte. Ausser einem Patienten benötigte keiner vagolytische oder sympathomimetische Medikamente, um Wirkungen auf alpha- oder beta-Rezeptoren von Labetolol in den darauffolgenden 24 h entgegenzuwirken.

LE LABETALOL I.V. DANS LE TRAITEMENT DE L'HYPERTENSION APRES CHIRURGIE DES ARTERES CORONAIRES

RESUME

Les effets cardiovasculaires de doses croissantes prédéterminées de labétalol ont été étudies chez 10 patients normovolémiques ayant reçu des sédatifs et présentant une hypertension et une tachycardie dans la période post-opératoire précoce après une revascularisation du myocarde. Une première dose de 20 mg était suffisante pour induire une diminution moyenne significative ($P < 0{,}01$) des pressions artérielles systoliques (−9,3%), diastolique (−8,2%) et moyenne (−7,9%) et du produit pression fréquence (PPF) (−13,1%). La fréquence cardiaque moyenne (FC) n'était pas significativement modifiée mais une corrélation linéaire pouvait être établie entre les modifications à 2 min et la valeur avant l'injection ($r = 0{,}73$). Une deuxième dose de labétalol (40 mg) administrée 5 min plus tard n'entraînait pas de diminution significative de la FC. La réponse individuelle variait beaucoup selon les patients et la gamme de doses totales efficaces park kg de poids corporel allait de 0,6 à 4,1 mg kg^{-1} (moyenne 2,2). A l'exception d'un patient, aucun sujet n'a eu besoin de vagolytiques ou de sympathomimétiques pour antagoniser les actions alpha ou beta de labétalol pendant les 24 h de la période d'étude.

LABETALOL I.M. EN EL TRATAMIENTO DE LA HIPERTENSIÓN DESPUES DE CIRUJÍA DE LA ARTERIA CORONARIA

SUMARIO

Se procedió a la evaluación de los efectos cardiovasculares de dosis i.v. crecientes fijas de labetalol administradas a 10 pacientes normovolémicos reposados que padecían de hipertensión y taquicardia en el periodo inmediato después de una revascularización miocárdiaca. Bastó con una primera dosis de 20 mg para provocar un descenso medio significante ($P < 0{,}01$) de la presión (AP) arterial media (−7,9%), sistólica (−9,3%) y diastólica (−8,2%) así como el producto presión–ritmo (RPP) (−13,1%). El ritmo cárdiaco medio (HR) no cambió de manera significante, pero pudo establecerse una correlación linear entre el cambio a los 2 min y el valor antes de la inyección ($r = 0{,}73$). Una segunda dosis de labetalol de 40 mg administrada 5 min después no hizo bajar más la AP, pero se observó una disminución significativa del HR. Se notó una diferencia marcada en la respuesta individual entre los pacientes según varíaba la gama de dosis totales efectivas por kg de peso corporal de 0,6 a 4,1 mg kg^{-1} (promedio 2,2). Salvo un solo paciente, ningún otro necesitó substancias vagolíticas o simpatomiméticas que se opusieran a las acciones alfa o beta del labetalol durante el periodo siguiente de 24 h.